REMARKS

Claims 1, 2 and 4-9 are pending in the application. By this Amendment, claim 1 is amended and claims 8 and 9 are cancelled.

Claim 1 is amended to remove references to neoplasia cells and limit the claims to vascular cells. No new matter is added.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience, Applicant's remarks are presented in the order in which they were raised in the Office Action.

A. Rejections Under 35 U.S.C. § 103

Clams 1-2, and 4-9 remain rejected under 35 U.S.C. § 103(a), as being unpatentable over Mendelsohn *et al.* ("Mendelsohn" U.S. Pat. No. 5,728,534) for the reasons of record set forth in the Office Action mailed 1/9/03. This rejection was mistakenly not included in the Office Actions mailed 7/2/03 and 5/5/04.

In particular, the Examiner points to col. 1, lines 43-63 to suggest that several classes of vasoprotective agents are described by Mendelsohn. The Examiner cites to col. 11, lines 37-59 of Mendelsohn for teaching "preferred vasoprotective agents decrease the expression of egr-1, as indicated by egr-1 (-/-)." (Office Action at page 3).

The Examiner admits that Mendelsohn does not indicate that the overall effect of decreasing egr-1 expression is the inhibition of vascular endothelial and smooth muscle cell proliferation, but states that it would have been obvious to test the ability of candidate vasoprotective agents accordingly.

Applicants respectfully traverse the Examiner's argument as an improper "obvious to try" rationale in support of an obviousness rejection.

> The admonition that 'obvious to try' is not the standard under § 103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior

> art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.....

In re O'Farrell, 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988) (citations omitted).

Mendelsohn fails to provide any teaching or suggestion that testing an agent which inhibited Egr-1 expression in vascular smooth muscle cells and vascular endothelial cells would **inhibit** proliferation of such cells if tested according to Mendelsohn's assay. Mendelsohn is directed to identifying agents which **activate** expression of estrogen responsive genes. For instance, col. 12, lines 25-27 of Mendelsohn states that "candidate vasoprotective agents" **activate** expression of estrogen responsive genes in vascular cells. Since Mendelsohn fails to provide any guidance that "the claimed result would be obtained if certain directions were pursued" the obviousness rejection over Mendelsohn is based on an improper "obvious to try" standard. (*See, In re Eli Lilly & Co.,* 902 F.2d 943, 14 U.S.P.Q.2d 1741 (Fed. Cir. 1990).

Further, Applicants submit that Mendelsohn does not teach or suggest a "method of screening for compounds which inhibit proliferation of vascular cells, the method comprising: (a) assessing an ability of a putative compound to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product; (b) assessing the ability of the putative compound to inhibit proliferation of vascular cells; and (c) selecting the putative compound that has been found to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product and inhibit proliferation of vascular cells" as specified in amended claim 1.

Applicants respectfully traverse the Examiner's conclusion on pages 2-3 of the Office Action that Mendelsohn discloses agents which activate expression of estrogen responsive genes in vascular cells (such as egr-1) to represent "only one embodiment" of vasoprotective agents. The Examiner relies on col. 11, lines 37-59 to assert that preferred vasoprotective agents of Mendelsohn decrease the expression of egr-1 in vascular endothelial cells and vascular smooth muscle cells, "as indicated by egr-1(-/-)." (*see* Mendelsohn 11:54).

However, Applicants submit that the Examiner's interpretation of the annotation "egr-1(-/-)" in Mendelsohn should be reconsidered in light of the Specification as a whole, and in particular,

at 3:41-4:65 and under the section "Reporters Based on Estrogen Responsive Genes" (11:16-12:24). In particular, the method disclosed in Mendelsohn requires the analysis to be based on differences in results observed in estrogen receptor-positive and estrogen receptor-negative cells.

The term "egr-1(-/-)" is defined by the format "preferred response in vascular endothelial cells / preferred response on vascular smooth muscle cells." (11:46-48) and the preferred response in each case is spelled out in several passages. (e.g., 4:34-42; 4:58-65).[1] When read in light of the Specification as a whole, the determination of the "egr-1(-/-)" response requires the summation of results from two different experiments:

1. a first experiment where the response of vascular endothelial cells (cells which express estrogen receptors) in terms of expression of egr-1 (an estrogen responsive gene) is determined relative to the expression of egr-1 in control "null" cells (which do not express estrogen receptors) in a manner described at col. 4, lines 19-42 of Mendelsohn; and
2. a second experiment where the response of vascular smooth cells (cells which express estrogen receptors) in terms of expression of egr-1 is similarly determined relative to the expression of egr-1 in control "null" cells (which do not express estrogen receptors) in a manner described at col. 4, lines 43-65 of Mendelsohn.

Alternatively, the "egr-1(-/-)" response is determined from the results of two similar experiments where "non-vascular cells" are used in place of "null" cells as cells which do not express estrogen receptors. (Mendelsohn 3:41– 4:18).

Clearly, the method taught by Mendelsohn to determine whether an agent is "egr-1(-/-)" is applicable **only** to agents which exert an effect on the expression of egr-1 by specifically acting upon estrogen receptors. The essential role of the estrogen receptors is evidenced by the comparisons discussed above as well as, the case of egr-1, requiring a differential reduction of egr-1

[1] For some specific targets, including egr-1, the preferred response according to Mendelsohn (11:48-59) is a decrease in expression, contrary to the methodology described in cols. 3 and 4.

in estrogen receptor-positive vascular endothelial cells and vascular smooth cells relative to estrogen receptor-negative null cells or non-vascular cells.

This limitation of egr-1 inhibitors acting through estrogen receptors as disclosed by Mendelsohn is different and non-obvious from the range of compounds to be screened by the method of claim 1. In particular, the screening method according to pending claim 1 allows identification of agents including those that act directly upon Egr-1 to inhibit induction of Egr-1 or decrease expression of Egr-1 or otherwise act on the Egr-1 gene product to bring about a decrease in the nuclear accumulation or activity of the Egr-1 gene product.

This distinction is highlighted in the Specification by the disclosure of antisense oligonucleotides and ribozymes as preferred agents targeted to Egr-1. (*see* Specification pages 14-16, 17-20). The assay according to Mendelsohn would not reveal such agents as "egr-1(-/-)" since they act directly on Egr-1 and would therefore inhibit induction of Egr-1 or decrease expression of egr-1 regardless of whether the cells upon which the agent is tested do or do not express estrogen receptors. Such directly acting agents would down regulate egr-1 in both vascular and null (or non-vascular) cells on the Mendelsohn method and would not be recognized as a "candidate vasoprotective agent" due to their lack of ability to distinguish between these two types of cells as required by Mendelsohn.

Mendelsohn relates to screening for vasoprotective agents based on distinguishing effects on estrogen receptor-positive and estrogen receptor-negative cells. Mendelsohn does not teach or suggest the screening method of claim 1 which selects agents suitable for inhibiting proliferation of vascular cells by mechanisms including inhibiting induction of Egr-1, decreasing expression of Egr-1, and decreasing nuclear accumulation or activity of the Egr-1 gene product. Therefore, Applicants respectfully request withdrawal of this ground for rejection under § 103(a) over Mendelsohn.

B. Rejections Under 35 U.S.C. § 102

Claims 1-2 and 8-9 are rejected under 35 U.S.C. § 102(b) as being anticipated by Sells et al. ("Sells"; Mol. Cell Biol. 15:682-692 (1995). In particular, Sells is cited for teaching the use of

antisense oligonucleotides targeting EGR-1 mRNA to reduce the expression of EGR-1 in *melanoma* cells. Claims 8 and 9 are cancelled and their rejection is moot.

Claim 1, as amended, specifies a "method of screening for compounds which inhibit proliferation of vascular cells, the method comprising: (a) assessing an ability of a putative compound to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product; (b) assessing the ability of the putative compound to inhibit proliferation of vascular cells; and (c) selecting the putative compound that has been found to inhibit induction of Egr-1, decrease expression of Egr-1 or decrease the nuclear accumulation or activity of the Egr-1 gene product and inhibit proliferation of vascular cells." (emphasis added). Claim 1 is amended to remove references to "neoplasia cells" and limit the claims to "vascular" cells. Sells relates only to melanoma cells.

Since melanoma cells are not vascular cells, Sells does not teach or suggest each and every limitation of claim 1, as amended. Sells does not anticipate independent claim 1. Claim 2 depends from claim 1. Therefore, Applicants respectfully request withdrawal of the rejection under 102(b) over Sells.

CONCLUSION

In view of the amendments and arguments set forth above, Applicants earnestly believe that they are entitled to a letters patent and respectfully request the Examiner to expedite prosecution of this patent application to issuance. Should the Examiner have any questions, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 529282000220. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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